Menopause and Hypothalamic-Pituitary Sensitivity to Estrogen

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Context The onset of human menopause is thought to be caused solely by ovarian failure and oocyte depletion. However, clinical symptoms and certain recent data in perimenopausal women suggest central nervous system involvement.

Objective To determine if modifications of hypothalamic-pituitary response to estrogen feedback mechanisms occur in older reproductive-age women as a mechanism of the onset of menopause.

Design, Setting, and Participants The Study of Women's Health Across the Nation (SWAN) is a multiethnic observational cohort study of the menopausal transition in 3302 women at 7 US sites. Of the subcohort of 840 women who participated in the Daily Hormone Study between 1997 and 1999, 680 women had evidence of luteal activity. The remaining 160 women (19%) did not have luteal activity and are the subject of this report.

Main Outcome Measures Daily urinary hormone levels of estrogen and progesterone metabolites, luteinizing hormone (LH), and follicle-stimulating hormone (FSH).

Results Three groups of women were studied: those with estrogen increases with an LH surge, those with estrogen increases without an LH surge, and those with neither. There were no differences in age or ethnicity among the 3 groups of women. Women in the third group (no increases) experienced more menopausal symptoms (hot flashes) than did women in the other groups with estrogen increases. In older reproductive-age women, the frequent existence of anovulatory cycles with estrogen peaks, equivalent to those that result in LH surges in younger women, yet in which no LH surges occur, indicates failure of estrogen-positive feedback on LH secretion. In other anovulatory cycles, follicular-phase estrogen levels did not lower LH secretion as occurs in cycles of younger women, indicating decreased estrogen-negative feedback on LH secretion.

Conclusion Our findings are compatible with hypothalamic-pituitary insensitivity to estrogen in aging perimenopausal women.

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BY THE YEAR 2030, MORE THAN 1.2 billion women in the world will be at least 50 years old.[1] This increasing proportion of the female population will be experiencing the menopausal transition with its accompanying physiology and pathophysiology. Reproductive aging in women and the hormonal changes that occur during the onset of human menopause have been ascribed solely to ovarian failure and oocyte depletion.[2] However, in other species, the central nervous system is the major regulator of age-related reproductive dysfunction.[3]

There are 4 events involving the hypothalamic-pituitary-ovarian axis that control the human menstrual cycle: (1) The secretion of follicle-stimulating hormone (FSH), responsible for the development of ovarian follicles and production of estradiol.[4] Throughout the cycle, estrogen maintains low gonadotropin levels via its negative feedback effect on hypothalamic gonadotropin-releasing hormone and consequently luteinizing hormone (LH) and FSH secretion.[5] (2) The FSH-induced increase in ovarian estrogen secretion to levels of sufficient strength and duration triggering an LH surge (positive feedback).[6] (3) The LH surge, a hypothalamic-pituitary response to the estrogen stimulus. This positive feedback response of estrogen on LH secretion has been used as a test of hypothalamic-pituitary function.[7,8] (4) Ovulation and luteinization of the follicle, triggered by the LH surge, forming a corpus luteum. This is an ovarian response that results in progesterone secretion necessary for the establishment of a pregnancy.[9]

How these events may be altered during menopausal transition has not been well established.

METHODS

The Study of Women's Health Across the Nation (SWAN) is a multiethnic observational cohort study of the menopausal transition in 3302 women at 7 sites across the United States designed to enhance understanding of the factors that influence the health of women of diverse race and ethnicity.[10] The details of enrollment have been previously reported.[10] Race/ethnicity was

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self-determined by study participants and was obtained by asking the following open-ended question: "How would you describe your primary racial or ethnic group?" The responses then were categorized as Caucasian (white), African American, Chinese, Japanese, or Hispanic. This study was approved by all of the sites' institutional review board, and written informed consent was obtained from each participant.

A subcohort participated in the Daily Hormone Study (DHS) from 1997 to 1999. The women in the DHS included 257 Caucasian (white) women, 175 African American women, 152 Chinese women, 170 Japanese women, and 86 women of Hispanic origin. The cohort has been described previously.[11,12] Inclusion criteria were age 42 to 52 years; an intact uterus and at least one ovary; at least one menstrual period in the prior 3 months; no use of sex-steroid hormones in the previous 3 months; and not being pregnant. DHS enrollees completed a daily collection of morning voided urine for an entire menstrual cycle ending in bleeding or to 50 days, whichever came first. During the cycle that they collected daily urine specimens, DHS enrollees also completed a daily diary, a questionnaire in which they answered, once a day, whether they had experienced within the preceding 24 hours any trouble sleeping and any hot flashes or night sweats.

Urinary LH, FSH, the estradiol urinary metabolites estrone conjugates (E1c), and the progesterone urinary metabolite pregnanediol glucuronide were measured using chemiluminescent assays as described previously.[11,12] Concentrations were normalized for creatinine excretion. Previous studies have demonstrated that urinary levels of these hormones, collected and measured by the methods used herein, mirror serum hormone patterns during the menstrual cycle in eumenorrheic controls so closely that patterns of serum and urinary gonadotropins and sex steroids are superimposible.[13]

Of the 840 women who completed the DHS study, 680 women had evidence of luteal activity based on a validated algorithm for pregnanediol glucuronide.[12] The algorithm locates the 5 nadir days of pregnanediol glucuronide in the follicular phase using moving averages throughout the cycle. A 3-fold increase in pregnanediol glucuronide concentrations above this nadir for at least 3 consecutive days was considered evidence of luteal activity. The cycles of these women have been reported previously.[12] The remaining 160 women (19% of the total 840 women) did not have luteal activity. One woman could not be subclassified due to missing data points. The 159 remaining women are the subjects of this report.

All women in the SWAN DHS study had levels of FSH equal to or greater than those previously demonstrated in younger women throughout the entire cycle.[12] This has been described previously and is due to the decreased secretion of ovarian inhibin in older women.[14,15] Decreased gonadotropin secretion, as is found in some anovulatory cycles in premenopausal young women in their teens to 30s, clearly did not occur in these women.

Conceptually, an estrogen increase is a high level compared with baseline, in absolute terms and relative to observed variability, followed by substantial decline. The specific criteria used here were adapted from previously established definitions for midreproductive age women.[13] An estrogen increase was defined as an E1c level of at least (1) 50 pg/mg creatinine, (2) twice the baseline level (the mean of 5 consecutive days starting 9 days earlier), and (3) 3 standard deviations of the baseline levels above the baseline mean. In addition, the estrogen peak was required to culminate in a drop to no more than 1.5 times baseline at some time within the next 5 days. An LH surge is considered present when a high level is observed relative to baseline in absolute terms and in excess of day to day variability both before and after the peak, established by a drop in levels. An LH surge was defined as an LH level of at least (1) 6 mIU/mg creatinine, (2) 3 times the mean baseline level (of 4 consecutive days starting 5 days earlier), (3) baseline mean plus 3 standard deviations of the 4-day baseline levels, (4) baseline mean plus 2 standard deviations of levels on days 2 through 6 after the peak, and (5) 0.8 times the maximum level in that cycle. In addition, the LH surge was required to culminate in a drop to no more than 1.5 times baseline within 6 days following the peak.

Cycles were classified by these algorithms as falling into 1 of 3 distinct patterns: (1) both estrogen increase and LH surge (coincident within 2 days), (2) estrogen increase only, and (3) neither. Visual inspection of the cycle data plots by 2 observers (G.W., J.H.S.) revealed that 20 cycles had apparent estrogen increases that were missed by the defining algorithm due to an increase too early in a short cycle to establish a baseline or a slow decline. Four cycles with an algorithmically determined estrogen increase were reclassified to "neither." Thus, of 159 cycles, 29 were classified as "both," 32 as "estrogen increase only," and 98 as "neither." These cycle classifications were based solely on hormone levels and not age or menopausal symptoms.

Analysis of variance was conducted to compare cycle classification groups on women's ages and body mass index; χ^2 tests were conducted to compare groups on ethnicity, reason for ending collection, and experience of symptoms during the cycle. Rank-sum tests were conducted to compare E1c levels of groups 1 and 2 by cycle day and to compare the 3 groups on women's percentage of cycle days with symptom occurrence. Reported *P* values are 2-sided, without adjustment for multiple comparisons. Statistical analyses were performed with SAS version 8.2 (SAS Institute, Cary, NC). Statistical significance was set at 2-sided $P<.05$.

RESULTS

Women in the 3 classification categories presented here were compared by ethnicity, age, and body mass index. As shown in TABLE 1, there was no

significant correlation between category of cycle and any of these characteristics.

The results from the 29 individuals who had an estrogen increase followed by an LH surge (group 1, "both") are shown in FIGURE 1, left panels, in which hormone levels are synchronized to the LH peak. As seen in ovulatory cycles, these LH surges are accompanied by FSH surges. Hormone levels are similar to those of the previously reported women in DHS who had luteal phases,[12] indicating an adequate hypothalamic-pituitary response. In women in group 1, the follicle or follicles that secreted sufficient estrogen to elicit an LH and FSH surge did not luteinize as documented by lack of an increase in pregnanediol glucuronide levels. This is a defect at the ovarian level because hypothalamic-pituitary responses were similar to those of women with apparently normal cycles.

The results from the 32 women who had clear estrogen increases but no LH surges (group 2) are shown in Figure 1, middle panel. Hormone levels are synchronized to the E1c peak because no LH surges were seen in these women. The estrogen increases in these women were equivalent to those seen in ovulatory women and to those in group 1. However, in contrast to those of group 1 women, these estrogen increases did not produce an LH surge. Comparisons of the E1c levels at each cycle day in group 1 women with those in group 2 women were performed using rank-sum tests. At all cycle days, E1c levels in group 2 women who had no LH surge were not lower than E1c levels in group 1 women who had LH surges. In fact, no differences at any cycle day were observed, with the exception of day −15, when E1c levels in group 2 women were higher ($P=.04$) than those in women in group 1.

That the secretion pattern of E1c in group 2 women was equivalent to that of women in group 1 is not apparent in Figure 1, in which hormone levels are synchronized to the LH surge as is convention. Therefore, the E1c levels synchronized to the E1c peak are presented in FIGURE 2. For ease of illustration of this similarity (between E1c levels in the women with gonadotropin surges and those in women without surges), the corresponding data for group 2 from Figure 1 are also provided in Figure 2. These E1c patterns in women in groups 1 and 2 are also similar to E1c secretion in the previously reported SWAN DHS study in women with luteal activity.[12] Thus, in group 2 women there is adequate ovarian response, but the LH surge, a hypothalamic-pituitary phenomenon, did not occur in the presence of an estrogen stimulus that is adequate to elicit an LH surge in ovulating women and in younger women. This clearly demonstrates unresponsiveness of the hypothalamic-pituitary axis to an estrogen peak. Gonadotropin levels dropped in the latter part of the cycles, likely due to negative feedback from the estrogen increase.

Hormone secretion in the 98 women who had no estrogen peaks or LH surges (group 3) are shown in Figure 1, right panels. Levels of LH are higher than those seen in either SWAN perimenopausal women with luteal phases or in the other 2 groups presented here. Estrogen levels are comparable to those in the early follicular phase of DHS luteal women[12] and group 1 or 2 women. Thus, group 3 women still have ovarian function but are unable to produce an estrogen peak.

Twenty-eight of the 29 women with LH surges (group 1), 31 of the 32 women without LH surges (group 2), and 97 of the 98 women with neither estrogen nor LH increases (group 3) participated in the daily diary component of the study. For each symptom—trouble sleeping or hot flashes or night sweats—the percentage of days a woman reported that she experienced the symptom was computed as the total number of days she reported presence of the symptom divided by the total number of days she reported either yes or no for that symptom × 100. These percentages of days with positive reports for women in the 3 categories were compared by rank-sum tests.

There were no differences in the percentages of days with trouble sleeping among the 3 groups (TABLE 2). Comparison of the percentages of days with hot flashes or night sweats among the 3 groups revealed significant group differences (Table 2). The percentages of days with hot flashes or night sweats were significantly higher for group 3 women than for either group 1 women ($P=.01$) or group 2 women ($P=.02$). The percentages of days with hot flashes or night sweats in group 1 women and group 2 women did not differ ($P=.73$).

Table 1. Characteristics of Women by Cycle Category*

	Cycle Category			
	1 (Estrogen Increase + LH Surge)	2 (Estrogen Increase Only)	3 (Neither Estrogen Nor LH Increase)	*P* Value†
No. of women	29	32	98	
Women with menses by cycle day 50, No. (%)	21 (72)	24 (75)	41 (42)	
Age, mean (SD), y	48 (2.5)	49 (2.5)	49 (2.6)	.10
BMI, mean (SD)	27 (6.8)	30 (7.4)	29 (8.2)	.59

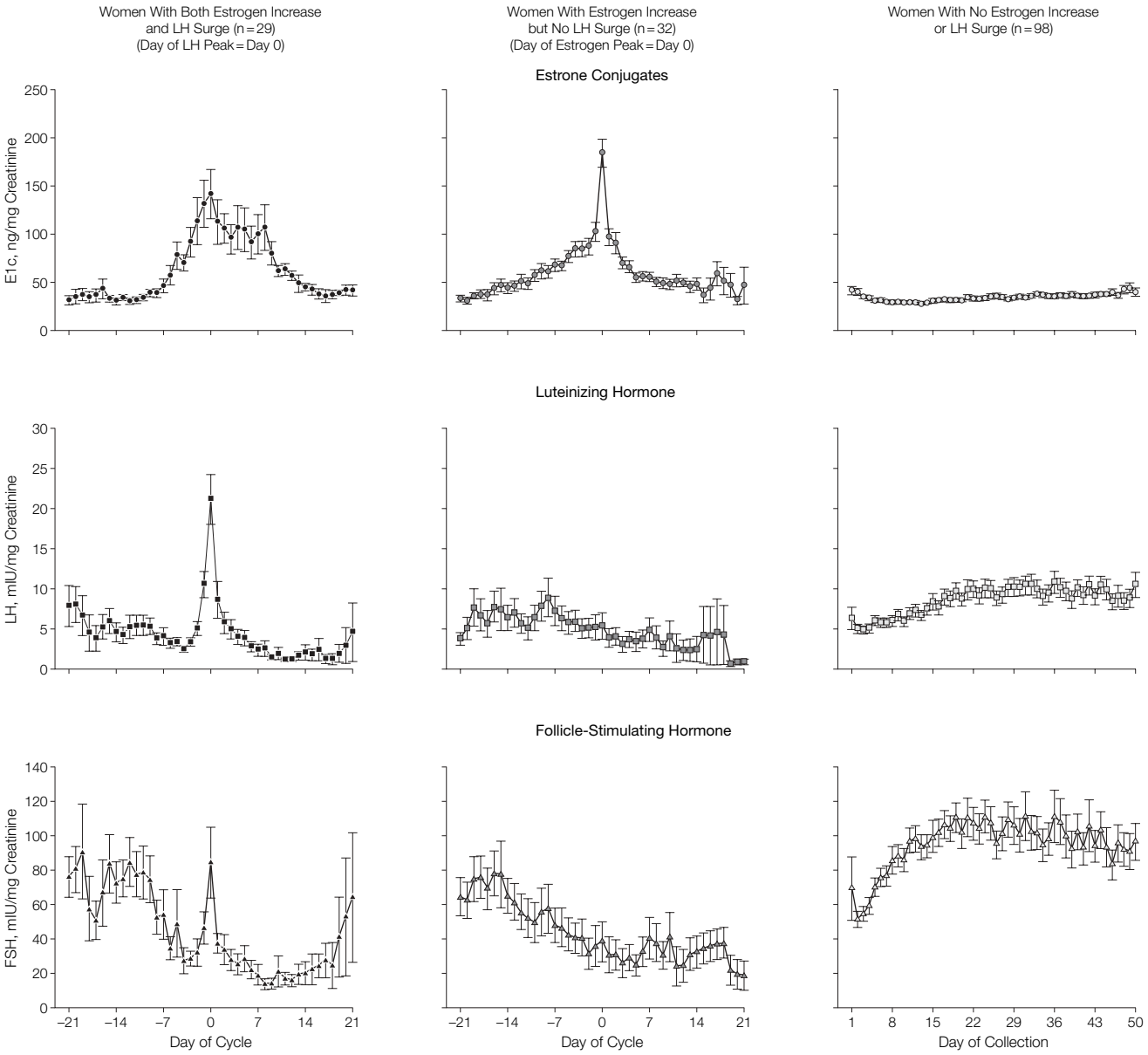
Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; LH, luteinizing hormone.
*Groups did not differ significantly by ethnicity ($P=.22$, χ^2, data not shown). Classification groups differ significantly in the reason for ending daily collection of samples: onset of menses or end of 50-day collection interval ($P<.001$, χ^2).
†Analysis of variance.

COMMENT

Hormone secretion patterns in older reproductive-age women demonstrate significant alterations of hypothalamic-pituitary feedback mechanisms in addition to decreased ovarian function. Cycles exist in which failure to mount an LH surge occurs in the face of adequate estrogen stimulation. These findings support the hypothesis that there is a relative hypothalamic-pituitary insensitivity to estrogen in ag-

ing women that is manifested by both positive and negative feedback mechanisms. Estrogen levels and patterns that produce LH surges in younger women fail to do so in some older women. In addition, levels of estrogen similar to those in younger women, which cause negative feedback of LH in normal ovulatory women and in group 1 women, fail to do so in group 3 women, who have elevated LH in the presence of early follicular-phase levels of E1c. This situation may represent a later stage of the menopausal transition because there is opening of the negative feedback loop between ovarian estrogen and pituitary LH, as is seen in postmenopausal women. Levels of estrogen capable of lowering LH in cycling women were not able to cause negative feedback of estrogen on LH secretion. Because control of FSH secretion is more complex than LH and includes major influences by inhibins and activins, FSH is not a

Figure 1. Daily Urinary Hormone Levels in Anovulatory Older Reproductive-Age Women With and Without Estrogen Increases



First morning voided urine samples were collected by each woman daily for an entire menstrual cycle or to 50 days. Levels of estrone conjugates (E1c), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and creatinine were measured in each sample. Hormone levels in each sample were normalized to creatinine values. Levels are presented as mean (SEM) plotted against cycle day, where day 0 is the day of the LH or estrogen peak for women with an estrogen increase. Mean (SEM) levels are plotted against day of collection for women with no estrogen increase.

good marker for estrogen-negative feedback control of gonadotropin secretion. Decreased LH pulse frequency has been observed in the presence of normal, midreproductive sex steroid levels in both the follicular[16] and luteal[17] phases of the menstrual cycles of older premenopausal women, supporting this hypothesis as well.

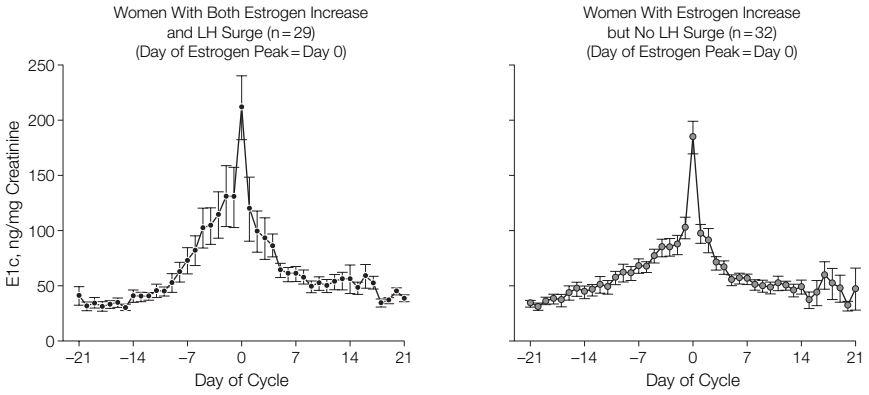
A predominant hypothesis to explain the onset of puberty is the occurrence of a gradual decrease in estrogen sensitivity of the hypothalamic-pituitary axis, such that small levels of circulating estrogen, which suppress gonadotropin secretion prepuberty, are unable to do so in the pubertal transition.[18] Decreased sensitivity in later life may simply be a continuation of the same pattern of progressive age-related estrogen insensitivity. Levels of LH are higher in perimenopausal women than in younger women, even in the presence of estrogen concentrations that result in lower LH levels in younger women.[14] Symptoms such as hot flashes and sleep disturbances occur more commonly in perimenopausal women than in postmenopausal women.[19] Yet, the perimenopausal transition is a time when circulating estrogen levels are equivalent or higher than levels observed in younger women.[14] Additionally, exogenous estrogen is therapeutic in perimenopausal women.[20] These observations are consistent with the hypothesis that a decrease in estrogen sensitivity occurs as women age through the menopausal transition.

We found no differences in reported symptoms of sleep disturbances or vasomotor changes in women with different LH-positive feedback responses to equivalent circulating estrogen peaks (categories 1 and 2). Although group 3 women did not differ in the prevalence of sleep disturbances, they had a significantly higher prevalence of hot flashes or night sweats. While all women in this study had similar baseline estrogen levels, the group 3 women did not have midcycle estrogen peaks. Since younger women with estrogen levels similar to these women[12] do not get hot flashes, the flashes may be due to opening of the negative feedback loop of estrogen on gonadotropin secretion.

All women have hormonal changes during their menopausal transition, but not all women experience symptoms. It is likely that the gonadotropin control centers in the brain differ from the areas involved in the symptoms assessed in our study. These regions may have different steroid sensitivities and control mechanisms, accounting for our findings. However, certain changes in gonadotropin levels may be permissive to alterations in central nervous system function, which result in symptoms. Physicians should be aware of the central nervous system changes involved in the menopausal transition because these changes best explain their patients' symptoms. An appreciation of these changes may assist patients in understanding and dealing with their own menopause. Other symptoms, such as mood and changes in affect, may also have similar explanations.

Demonstration of hypothalamic-pituitary insensitivity to estrogen in perimenopausal women shows that certain human menopausal responses are similar to those of other species, including rats. Age-related decreased expression of estrogen receptor β in some hypothalamic areas in the rat has been described.[21] These results suggest that the rat may be a useful model for the study of human central nervous system aging and that the mechanisms of reproductive aging may be more similar in diverse mammalian species than previously thought.

Figure 2. Daily Urinary E1c Levels in Anovulatory Older Reproductive-Age Women With Estrogen Increases



Comparison of E1c levels (estrone conjugates) in women who had an LH surge (group 1) (left panel) vs those who did not (group 2) (right panel). E1c levels (mean [SEM]) for women with both estrogen increases and LH surges are shown here, where day 0 is the day of maximum E1c.

Table 2. Daily Diary Symptom Reporting

	Cycle Category			
	1 (Estrogen Increase + LH Surge)	2 (Estrogen Increase Only)	3 (Neither Estrogen Nor LH Increase)	*P* Value
No. of women	28	31	97	
Trouble sleeping, mean % of days in cycle	21	22	23	.93*
Hot flashes or night sweats				
Mean % of days in cycle	9	11	26	.009*
Women not experiencing, No. (%)	15 (54)	15 (48)	34 (35)	.14†

Abbreviation: LH, luteinizing hormone.
*Rank-sum test.
†χ^2 test.

Author Contributions: Dr Weiss had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Weiss, Skurnick, Goldsmith, Santoro, Park.
Acquisition of data: Weiss, Santoro.
Analysis and interpretation of data: Weiss, Skurnick, Goldsmith, Santoro, Park.
Drafting of the manuscript: Weiss, Skurnick, Goldsmith, Park.
Critical revision of the manuscript for important intellectual content: Weiss, Skurnick, Goldsmith, Santoro, Park.
Statistical analysis: Skurnick.
Obtained funding: Weiss, Skurnick, Santoro.
Administrative, technical, or material support: Weiss, Goldsmith, Santoro, Park.
Study supervision: Weiss, Santoro.
SWAN Clinical Centers: University of Michigan, Ann Arbor: MaryFran Sowers, PI (U01 NR04061); Massachusetts General Hospital, Boston: Robert Neer, PI 1995-1999, Joel Finkelstein, PI 1999- present (U01 AG012531); Rush University, Rush-Presbyterian-St Luke's Medical Center, Chicago, Ill: Lynda Powell, PI (U01 AG012505); University of California, Davis/Kaiser: Ellen Gold, PI (U01 AG012554); University of California, Los Angeles: Gail Greendale, PI (U01 AG012539); University of Medicine and Dentistry/New Jersey Medical School, Newark: Gerson Weiss, PI 1995-2004, Nanette Santoro, PI, 2004-present (U01 AG012535); and the University of Pittsburgh, Pittsburgh, Pa: Karen Matthews, PI (U01 AG012546).
NIH Program Office: National Institute on Aging, Bethesda, Md: Sherry Sherman, 1994-present, Marcia Ory, 1994-2001; National Institute of Nursing Research, Bethesda, Md: Janice Phillips, 2002-present, Carole Hudgings, 1997-2002.
Central Laboratory: University of Michigan, Ann Arbor: Rees Midgley, PI 1995-2000, Daniel McConnell, 2000-present (U01 AG012495, Central Ligand Assay Satellite Services).
Coordinating Centers: University of Pittsburgh, Pittsburgh, Pa: Kim Sutton-Tyrrell, PI (U01 AG012546) 2001-present and New England Research Institutes, Watertown, Mass: Sonja McKinlay, PI (U01 AG012553), 1995-2001.
Steering Committee: Chris Gallagher, Chair, 1995-1997; Jenny Kelsey, Chair, 1997-2002; Susan Johnson, Chair, 2002- present.
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Role of the Sponsor: The National Institute on Aging funded the SWAN study. The current study used data generated by the SWAN Daily Hormone Study (DHS). The DHS was designed and approved by the SWAN Steering Committee. The design and conduct of the current study were a product of the authors and the samples were collected according to the SWAN DHS protocol and occurred at all 7 clinical sites. Data management was performed by the SWAN Coordinating Center. Analysis and interpretation of the data were accomplished by the authors. Preparation of the manuscript was performed by the authors. The SWAN Presentation and Publication Committee reviewed and approved the concept, study plan, and manuscript draft for consistency with the SWAN study and appropriateness of the current work in accordance with SWAN policy.
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ming sperm."[1] This description is supremely felicitous, as the Veil Nebula is, in fact, the tattered remnants of a supernova—an exploding star.

But there is a far deeper connection. The universe started with little other than hydrogen and helium, and none of the heavy elements of our familiar world and ourselves. The heavier elements up through iron are produced inside massive stars much heavier than the sun, by thermonuclear fusion during the stable portions of their lives. When such stars reach the end of their useable nuclear fuel, they become unable to sustain their own weight, collapse, and rebound in a titanic explosion. This blast, occupying the last few seconds of the star's existence, synthesizes the elements heavier than iron and blows the entire star, aside from the core, into free space, where the heavy elements enrich the hydrogen and helium of the pristine interstellar medium. The next generation of stars and planetary systems born of the enriched gas thereby possesses the heavy elements required for the formation of solid planets and for life. Thus are we all, as astrophysicists and songwriters are wont to say, stardust. In this sense, the supernova actually is how "life begins."

The portion shown in the (much overexposed) photograph in the painting is called the Western Veil and is part of a larger complex called the Cygnus Loop, which is about 15 000 years old, 2500 light years away, 4 times the apparent diameter of the full moon, but very faint. Examined at leisure through a large telescope, under dark and transparent skies, the Veil Nebula is a complex, subtle, and sublime sight. Excellent photographs of the Veil Nebula can be found at the Web site of the National Optical Astronomy Observatories.[2]

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1. Southgate MT. The Cover. *JAMA*. 2004;292:1012.
2. Veil Nebula image gallery. National Optical Astronomy Observatories Web site. Available at: http://www.noao.edu/image_gallery/html/im0852.html. Accessibility verified November 30, 2004.

Rhesus Pieces

To the Editor: I read with interest the analysis of the stylistic aspects of the artwork of Wassily Kandinsky,[1] but felt that the geometric analysis regarding *Untitled Improvisation III* on the cover of the September 15, 2004, issue of *JAMA* sacrificed the whole at the expense of its parts, and in so doing Kandinsky makes a monkey out of all of us. Just take a second look and see if you don't agree.

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1. Southgate MT. The Cover. *JAMA*. 2004;292:1274.

CORRECTIONS

Data Error: In the Editorial titled "Stenting Small Coronary Arteries: Works in Progress" published in the December 8, 2004, issue of the JOURNAL (2004;292:2777-2778), an incorrect number was published. On page 2777 at the bottom of the first column, the percentage of patients in the sirolimus stent group with diabetes mellitus should read 19% (not 9%).

Error in Table: In the Original Contribution entitled "Familial Risk of Lung Carcinoma in the Icelandic Population" published in the December 22/29, 2004, issue of THE JOURNAL (2004;292:2977-2983), there was an error in Table 4. On page 2981, the second and fourth column headings, "Δ RR of Lung Carcinoma – Δ RR of Smoking" should have read "RR of Lung Carcinoma – RR of Smoking."

Funding Omissions: In the Original Contribution titled "Menopause and Hypothalamic-Pituitary Sensitivity to Estrogen" published in the December 22/29, 2004, issue of the JOURNAL (2004;292:2991-2996), the funding statement was incomplete. The paragraph should read:

Funding/Support: The Study of Women's Health Across the Nation (SWAN) was funded by the National Institute on Aging, the National Institute of Nursing Research, and the NIH Office of Research on Women's Health.

In addition, the NIH Program Office paragraph was incomplete. It should read:

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